# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

**Application Number : 040174**

**Trade Name : LEUCOVORIN CALCIUM FOR INJECTION 350MG/VIAL (BASE)**

**Generic Name: Leucovorin Calcium for Injection 350mg/vial (base)**

**Sponsor : Gensia Laboratories, Inc.**

**Approval Date: June 12, 1997**

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION 040174

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| | Included | Pending Completion | Not Prepared | Not Required |
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| Tenative Approval Letter | | | | |
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| Final Printed Labeling | X | | | |
| Medical Review(s) | | | | |
| Chemistry Review(s) | X | | | |
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| Pharmacology Review(s) | | | | |
| Statistical Review(s) | | | | |
| Microbiology Review(s) | | | | |
| Clinical Pharmacology Biopharmaceutics Review(s) | | | | |
| Bioequivalence Review(s) | X | | | |
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| | | | | |

# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number 040174**

# APPROVAL LETTER

DW

ANDA 40-174

Gensia Laboratories, Inc.
Attention: Donald J. Harrigan, R.Ph.
19 Hughes
Irvine, CA 92718

Dear Sir:

This is in reference to your abbreviated new drug application dated December 29, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Leucovorin Calcium for Injection, 350 mg/vial (base).

Reference is made to your amendment dated January 31, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Leucovorin Calcium for Injection, 350 mg/vial to be bioequivalent and therefore, therapeutically equivalent to that of the listed drug (Leucovorin Calcium for Injection, 350 mg/vial of Immunex Corporation).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign, at the time of their initial use, be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 040174

## FINAL PRINTED LABELING

# NDC 0703-5145-01
# Container Label
## (Part No. Y29-514-501)

## 350 mg/vial

Y29514501 JUN 12 1997

GENSIA®
LABORATORIES, LTD.
Oncology Products
N 0703-5145-01
**Leucovorin Calcium**
**For Injection**
*equivalent to Leucovorin*
**350 mg/vial**
For IM or IV Use
STERILE

When reconstituted with 17 mL of sterile diluent, the resulting solution will contain: Leucovorin Calcium equivalent to 20 mg Leucovorin per mL; Sodium Chloride 8.2 mg/mL; Sodium Hydroxide and/or Hydrochloric Acid qs to adjust pH to approximately 6.5-8.5. • Contains no preservative. Reconstitute with 17 mL Bacteriostatic Water for Injection, USP and use within 7 days or with Sterile Water for Injection, USP and use immediately. • Usual Dosage: See Insert for dosage and reconstitution information. Do not use preservative containing solution for doses greater than 10 mg/m² (See WARNINGS).

**Store dry product and reconstituted solution at controlled room temperature 15°-30°C (59°-86°F). • Protect from light. Store in carton until contents are used.**

**Do not use reconstituted product after** _____.

CAUTION: Federal (USA) law prohibits dispensing without prescription.

Gensia Laboratories, Ltd., Irvine CA 92618 Y29-514-501

GENSIA®
LABORATORIES, LTD.

Oncology Products

N0703-5145-01

# Leucovorin Calcium

## For Injection

*equivalent to Leucovorin*

## 350 mg/vial

**For IM or IV Use**

**STERILE**

When reconstituted with 17 mL of sterile diluent, the resulting solution will contain: Leucovorin Calcium equivalent to 20 mg Leucovorin per mL; Sodium Chloride 8.2 mg/mL; Sodium Hydroxide and/or Hydrochloric Acid qs to adjust pH to approximately 6.5-8.5. • Contains no preservative. Reconstitute with 17 mL Bacteriostatic Water for Injection, USP and use within 7 days or with Sterile Water for Injection, USP and use immediately. • Usual Dosage: See Insert for dosage and reconstitution information. Do not use preservative containing solution for doses greater than 10 mg/m$^2$ (See WARNINGS).

**Store dry product and reconstituted solution at controlled room temperature 15°-30°C (59°-86°F). • Protect from light. Store in carton until contents are used.**

GENSIA®
LABORATORIES, LTD.

Oncology Products

N0703-5145-01

Leucovorin Calcium

For Injection

*equivalent to Leucovorin*

350 mg/vial

For IM or IV Use

STERILE

See bottom panel for Lot Number and Expiration Date.

**CAUTION:** Federal (USA) law prohibits dispensing without prescription.

X12-514-501

Gensia Laboratories, Ltd., Irvine CA 92618

JUN 12 1997

GENSIA®
LABORATORIES, LTD.

Leucovorin Calcium

For Injection

*equivalent to Leucovorin*

350 mg/vial

Y36-202-103
Package Insert

JUN 12 1997

GENSIA®
LABORATORIES, LTD.

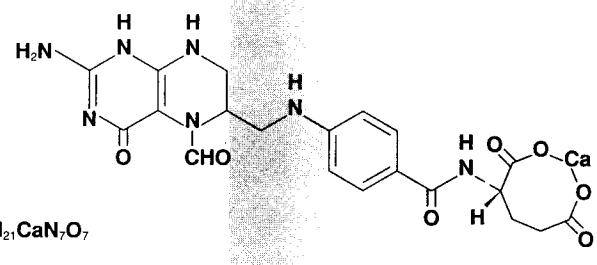
Oncology Products

# Leucovorin Calcium
## For Injection

**DESCRIPTION**

Leucovorin is one of several active, chemically reduced derivatives of folic acid. It is useful as an antidote to drugs which act as folic acid antagonists.

Also known as folinic acid, Citrovorum factor, or 5-formyl-5,6,7,8-tetrahydrofolic acid, this compound has the chemical designation of calcium *N*-[4-[[(2-amino-5-formyl-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)-methyl]amino]benzoyl]-L-glutamic acid (1:1). Leucovorin calcium has a molecular weight of 511.51 and the following structural formula:



$C_{20}H_{21}CaN_7O_7$

Leucovorin Calcium for Injection is a sterile product indicated for intravenous or intramuscular administration and is supplied in 100 and 350 mg vials.

Each 100 mg/vial of Leucovorin Calcium for Injection, when reconstituted with 10 mL of sterile diluent, will contain leucovorin calcium equivalent to 10 mg leucovorin per mL, sodium chloride 8mg/mL, sodium hydroxide and/or hydrochloric acid to adjust pH approximately 6.5-7.5.

Each 350 mg/vial of Leucovorin Calcium for Injection, when reconstituted with 17 mL of sterile diluent, will contain leucovorin calcium equivalent to 20 mg leucovorin per mL, sodium chloride 8.2 mg/mL, sodium hydroxide and/or hydrochloric acid to adjust pH to approximately 6.5-8.5.

The dry product contains no preservative. Reconstitute with Bacteriostatic Water for Injection, USP which contains benzyl alcohol (*see* **Warnings** section), or with Sterile Water for Injection, USP.

Leucovorin Calcium for Injection is a sterile, lyophilized powder.

There is 0.004 mEq of calcium per mg of leucovorin.

**CLINICAL PHARMACOLOGY**

Leucovorin is a mixture of the diastereoisomers of the 5-formyl derivative of tetrahydrofolic acid (THF). The biologically active compound of the mixture is the (-)-*ℓ*-isomer, known as Citrovorum factor or (-)-folinic acid. Leucovorin does not require reduction by the enzyme dihydrofolate reductase in order to participate in reactions utilizing folates as a source of "one-carbon" moieties. *ℓ*-Leucovorin (*ℓ*-5-formyltetrahydrofolate) is rapidly metabolized (via 5, 10-methenyltetrahydofolate then 5, 10-methylenetetrahydrofolate) to 1, 5-methyltetrahydrofolate. 1, 5-Methyltetrahydrofolate can in turn be metabolized via other pathways back to 5, 10, methylenetetrahydrofolate, which is converted to 5-methyltetrahydrofolate by an irreversible, enzyme catalyzed reduction using the cofactors $FADH_2$ and NADPH.

Administration of leucovorin can counteract the therapeutic and toxic effects of folic acid antagonists, such as methotrexate, which act by inhibiting dihydrofolate reductase.

In contrast, leucovorin can enhance the therapeutic and toxic effects of fluoropyrimidines used in cancer therapy, such as 5-fluorouracil. Concurrent administration of leucovorin does not appear to alter the plasma pharmacokinetics of 5-fluorouracil. 5-Fluorouracil is metabolized to fluorodeoxyuridylic acid, which binds to and inhibits the enzyme thymidylate synthase (an enzyme important in DNA repair and replication).

Leucovorin is readily converted to another reduced folate, 5, 10-methylenetetrahydrofolate, which acts to stabilize the binding of fluorodeoxyridylic acid to thymidylate synthase and thereby enhances the inhibition of this enzyme.

The pharmacokinetics after intravenous and intramuscular administration of a 25 mg dose of leucovorin were studied in male volunteers. After intravenous administration, serum total reduced folates (as measured by *Lactobacillus casei* assay) reached a mean peak of 1259 ng/mL (range 897 to 1625). The mean time to peak was 10 minutes. This initial rise in total reduced folates was primarily due to the parent compound 5-formyl-THF (measured by *Streptococcus faecalis* assay) which rose to 1206 ng/mL at 10 minutes. A sharp drop in parent compound followed and coincided with the appearance of the active metabolite 5-methyl-THF which became the predominant circulating form of the drug.

The mean peak of 5-methyl-THF was 258 ng/mL and occurred at 1.3 hours. The terminal half-life for total reduced folates was 6.2 hours. The area under the concentration versus time curves (AUCs) for *ℓ*-leucovorin, *d*-leucovorin, and 5-methyltetrahydrofolate were 28.4 ± 3.5, 956 ± 97 and 129 ± 12 (mg.min/L ± S.E.). When a higher dose of *d, ℓ*-leucovorin (200mg/m$^2$) was used, similar results were obtained. The *d*-isomer persisted in plasma at concentrations greatly exceeding those of the *ℓ*-isomer.

After intramuscular injection, the mean peak of serum total reduced folates was 436 ng/mL (range 240 to 725) and occurred at 52 minutes. Similar to IV administration, the initial sharp rise was due to the parent compound. The mean peak of 5-formyl-THF was 360 ng/mL and occurred at 28 minutes. The level of the metabolite 5-methyl-THF increased subsequently over time until at 1.5 hours it represented 50% of the circulating total folates. The mean peak of 5-methyl-THF was 226 ng/mL at 2.8 hours. The terminal half-life of total reduced folates was 6.2 hours. There was no difference of statistical significance between IM and IV administration in the AUC for total reduced folates, 5-formyl-TH, or 5-methyl-THF.

**INDICATION AND USAGE**

Leucovorin calcium rescue is indicated after high-dose methotrexate therapy in osteosarcoma.

Leucovorin Calcium for Injection is indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosages of folic acid antagonists.

Leucovorin calcium is indicated in the treatment of megaloblastic anemias due to folic acid deficiency when oral therapy is not feasible.

**CONTRAINDICATIONS**

Leucovorin is improper therapy for pernicious anemia and other megaloblastic anemias secondary to the lack of vitamin $B_{12}$. A hematologic remission may occur while neurologic manifestations continue to progress.

**WARNINGS**

In the treatment of accidental overdosages of folic acid antagonists, leucovorin should be administered as promptly as possible. As the time interval between antifolate administration (e.g., methotrexate) and leucovorin rescue increases, leucovorin's effectiveness in counteracting toxicity decreases. Do not administer leucovorin intrathecally.

Monitoring the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

Delayed methotrexate excretion may be caused by a third space fluid accumulation (i.e., ascites, pleural effusion), renal insufficiency, or inadequate hydration. Under such circumstances, higher doses of leucovorin or prolonged administration may be indicated. Doses higher than those recommended for oral use must be given intravenously.

Because of the benzyl alcohol contained in certain diluents used for reconstituting Leucovorin Calcium for Injection, when doses greater than 10 mg/m$^2$ are administered, Leucovorin Calcium for Injection should be reconstituted with Sterile Water for Injection, USP and used immediately (*see* **Dosage and Administration**).

Because of the calcium content of the leucovorin solution, no more that 160 mg of leucovorin should be injected intravenously per minute (16 mL of a 10 mg/mL, or 8 mL of a 20 mg/mL solution per minute).

Leucovorin enhances the toxicity of 5-fluorouracil. When these drugs are administered concurrently, the dosage of the 5-fluorouracil must be lower than usually administered. Although the toxicities observed in patients treated with the combination of leucovorin plus 5-fluorouracil are qualitatively similar to those observed in patients treated with 5-fluorouracil alone, gastrointestinal toxicities (particularly stomatitis and diarrhea) are observed more commonly and may be more severe and of prolonged duration in patients treated with the combination.

Therapy with leucovorin and 5-fluorouracil must not be initiated or continued in patients who have symptoms of gastrointestinal toxicity of any severity, until those symptoms have completely resolved. Patients with diarrhea must be monitored with particular care until the diarrhea has resolved, as rapid clinical deterioration leading to death can occur. In a study utilizing higher weekly doses of 5-FU and leucovorin, elderly and/or debilitated patients were found to be at greater risk for severe gastrointestinal toxicity.[1]

**PRECAUTIONS**

**General:** Parenteral administration is preferable to oral dosing if there is a possibility that the patient may vomit or not absorb the leucovorin. Leucovorin has no effect on non-hematologic toxicities of methotrexate such as the nephrotoxicity resulting from drug and/or metabolite precipitation in the kidney.

**Drug Interactions:** Folic acid in large amounts may counteract the antiepileptic effect of phenobarbital, phenytoin and primidone, and increase the frequency of seizures in susceptible children.

Preliminary animal and human studies have shown that small quantities of systemically administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1 to 3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Leucovorin may enhance the toxicity of 5-fluorouracil (*see* **Warnings**).

**Pregnancy:** Teratogenic Effects:

"Pregnancy Category C." Adequate animal reproduction studies have not been conducted with leucovorin. It is also not known whether leucovorin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Leucovorin should be given to a pregnant woman only if clearly needed.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when leucovorin is administered to a nursing mother.

**Pediatric Use:** See **Drug Interactions**.

**ADVERSE REACTIONS**

Allergic sensitization, including anaphylactoid reactions and urticaria, has been reported following the administration of both oral and parenteral leucovorin. No other adverse reactions have been attributed to the use of leucovorin *per se*.

## OVERDOSAGE

Excessive amount of leucovorin may nullify the chemotherapeutic effect of folic acid antagonists.

## DOSAGE AND ADMINISTRATION

**Leucovorin Rescue After High-Dose Methotrexate Therapy:** The recommendations for leucovorin rescue are based on a methotrexate dose of 12 to 15 grams/m$^2$ administered by intravenous infusion over 4 hours (See methotrexate package insert for full prescribing information).[2] Leucovorin rescue at a dose of 15 mg (approximately 10 mg/m$^2$) every 6 hours for 10 doses starts 24 hours after the beginning of the methotrexate infusion. In the presence of gastrointestinal toxicity, nausea or vomiting, leucovorin should be administered parenterally. Do not administer leucovorin intrathecally.

Serum creatinine and methotrexate levels should be determined at least once daily. Leucovorin administration, hydration, and urinary alkalinization (pH of 7.0 or greater) should be continued until the methotrexate level is below 5 x $10^{-8}$ M (0.05 micromolar). The leucovorin dose should be adjusted or leucovorin rescue extended based on the following guidelines:

**GUIDELINES FOR LEUCOVORIN DOSAGE ADMINISTRATION**
**DO NOT ADMINISTER LEUCOVORIN INTRATHECALLY**

| Clinical Situation | Laboratory Findings | Leucovorin Dosage And Duration |
|---|---|---|
| Normal Methotrexate Elimination | Serum methotrexate level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0.2 micromolar at 72 hours. | 15 mg PO, IM, or IV q 6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion). |
| Delayed Late Methotrexate Elimination | Serum methotrexate level remaining above 0.2 micromolar at 72 hours, and more than 0.05 micromolar at 96 hours after administration. | Continue 15 mg PO, IM, or IV q 6 hours, until methotrexate level is less than 0.05 micromolar. |
| Delayed Early Methotrexate Elimination and/or Evidence of Acute Renal Injury | Serum methotrexate level of 50 micromolar or more at 24 hours, or 5 micromolar or more at 48 hours after administration, OR; a 100% or greater increase in serum creatinine level at 24 hours after methotrexate administration (eg, an increase from 0.5 mg/dL to a level of 1 mg/dL or more). | 150 mg IV q 3 hours, until methotrexate level is less than 1 micromolar; then 15 mg IV q 3 hours until methotrexate level is less than 0.05 micromolar. |

Patients who experience delayed early methotrexate elimination are likely to develop reversible renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalinization, and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 micromolar and the renal failure has resolved.

Some patients will have abnormalities in methotrexate elimination or renal function following methotrexate administration, which are significant but less severe than abnormalities described in the table above. These abnormalities may or may not be associated with significant clinical toxicity. If significant clinical toxicity is observed, leucovorin rescue should be extended for an additional 24 hours (total of 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medications which interact with methotrexate (eg, medications which may interfere with methotrexate elimination or binding to serum albumin) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

**Impaired Methotrexate Elimination or Inadvertent Overdosage:**
Leucovorin rescue should begin as soon as possible after an inadvertent overdosage and within 24 hours of methotrexate administration when there is a delayed excretion (*see* **Warnings**). Leucovorin 10 mg/m$^2$ should be administered IV, IM, or PO every 6 hours until the serum methotrexate level is less than $10^{-8}$M. In the presence of gastrointestinal toxicity, nausea, or vomiting, leucovorin should be administered parenterally. Do not administer leucovorin intrathecally.

Serum creatinine and methotrexate levels should be determined at 24 hour intervals. If the 24 hour serum creatinine has increased 50% over baseline, or if the 24 hour methotrexate level is greater than 5 x $10^{-6}$M, or the 48 hour level is greater than 9 x $10^{-7}$M, the dose of leucovorin should be increased to 100 mg/m$^2$ IV every 3 hours until the methotrexate level is less than $10^{-8}$M.

Hydration (3L/d) and urinary alkalinization with sodium bicarbonate solution should be employed concomitantly. The bicarbonate dose should be adjusted to maintain the urine pH at 7.0 or greater.

**Megalobastic Anemia Due to Folic Acid Deficiency:**
Up to 1 mg daily. There is no evidence that doses greater than 1 mg/day have greater efficacy than those of 1 mg; additionally, loss of folate in urine becomes roughly logarithmic as the amount administered exceeds 1 mg.

**Preparation:** Each 100 mg vial of Leucovorin Calcium for Injection when reconstituted with 10 mL of sterile diluent yields a leucovorin concentration of 10 mg per mL. Each 350 mg vial of Leucovorin Calcium for Injection when reconstituted with 17 mL of sterile diluent, yields a leucovorin concentration of 20 mg leucovorin per mL. Leucovorin Calcium for Injection contains no preservative. Reconstitute with Bacteriostatic Water for Injection, USP, which contains benzyl alcohol, or with Sterile Water for Injection, USP. When reconstituted with Bacteriostatic Water for Injection, USP, the resulting solution must be used within 7 days. If the product is reconstituted with Sterile Water for Injection, USP, it must be used immediately.

Because of the benzyl alcohol contained in Bacteriostatic Water for Injection, USP, when doses greater than 10 mg/m$^2$ are administered, Leucovorin Calcium for Injection should be reconstituted with Sterile Water for Injection, USP and used immediately (*see* **Warnings**).

Because of the calcium content of the leucovorin solution, no more than 160 mg of leucovorin should be injected intravenously per minute (16 mL of a 10 mg/mL, or 8 mL of a 20 mg/mL solution per minute).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

## HOW SUPPLIED

Leucovorin Calcium for Injection equivalent to 100 mg or 350 mg Leucovorin per vial is available as follows:

| | |
|---|---|
| N0703-**5140-01** | 100 mg vial packaged individually |
| N0703-**5145-01** | 350 mg vial packaged individually |

Store dry product and reconstituted solution at controlled room temperature 15°-30°C (59°-86°F). **Protect from light. Store in carton until contents are used.**

**CAUTION:** Federal (USA) law prohibits dispensing without prescription.

## REFERENCES:


1. Grem, J.L., Shoemaker, D.D., Petrelli, N.J., Douglas, H.O., "Severe and Fatal Toxic Effects Observed in Treatment with High- and Low-Dose Leucovorin Plus 5-Fluorouracil for Colorectal Carcinoma," *Cancer Treat Rep* 1987; 71:1122.
2. Link MP, Goorin AM, Miser AW, et al, "The Effect of Adjuvant Chemotherapy on Relapse-Free Survival in Patients with Osteosarcoma of the Extremity." *N Engl J Med* 1986; 314:1600-1606.



Gensia Laboratories, Ltd.
Irvine, CA 92618
Revised: January 1997

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 040174

## CHEMISTRY REVIEW(S)

# Office of Generic Drugs

## Chemistry, Manufacturing and Controls Review

1. **REVIEW NUMBER**: Chemistry Review No. 3

2. **ANDA**: 40-174

3. **NAME AND ADDRESS OF APPLICANT**:
   Gensia Laboratories, Inc.
   Attention: Donald J. Harrigan
   19 Hughes
   Irvine, CA 92618

4. **LEGAL BASIS FOR ANDA SUBMISSION**: See CR #1.

5. **SUPPLEMENT(S)**: N/A  6. **DRUG NAME**: N/A

7. **NONPROPRIETARY NAME**: Leucovorin Calcium for Injection

8. **SUPPLEMENT(S) PROVIDE(S) FOR**: N/A

9. **AMENDMENTS AND OTHER DATES**:

   Gensia:

| | |
|---|---|
| 12/29/95 | ANDA submission (received on 12/29/96) |
| 02/15/96 | Amendment (response to refuse to File) |
| 09/12/96 | Response to NA letter dated 06/24/96 |
| 01/31/97* | Response to NA fax dated 01/15/97 |

   FDA:

| | |
|---|---|
| 02/02/96 | Refuse to File letter |
| 03/11/96 | Acknowledge of submission. (date acceptable for filing: 02/16/96) |
| 06/24/96 | NA (FAX) fax (From CR #1 by S.Liu) |
| 01/15/97 | NA (MINOR) letter (From CR #2 by S.Liu) |

10. **PHARMACOLOGIC CATEGORY**: See CR #1.

11. **HOW DISPENSED**: Rx

12. **RELATED INDs, NDAs and DMFs**: See CR #1.

13. **DOSAGE FORM**: Lyophilized, injectable

14. **POTENCY AFTER RECONSTITUTION**: 20 mg/mL (350 mg/vial)

15. **CHEMICAL STRUCTURE AND NAME**: See CR #1

16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS:**
The drug substance has a USP monograph. The drug product is not a subject of the USP 23 (up to Supplement 5).

Gensia already has two approved ANDAs for this drug product of different strengths: 81-277 (100 mg/vial), 81-278 (50 mg/vial). However, Gensia indicates in the current labeling section of the ANDA that they do not supply 50 mg (ANDA 81-278) currently.

The labeling review is completed, and there are no deficiencies. Bio review was satisfactory, and a bio acceptance letter was sent on 06/27/96. EER is still pending.

The (b)4 method for assay and impurities monitoring is the same method for approved ANDA 81-277 and 81-278. Since the District Laboratory previously validated the method, there is no need to request a re-validation.

Microbiologist's review is completed, and was satisfactory. It was signed off on 12/10/96.

Gensia's response to the only remaining chemistry deficiency regarding their inspection level for lyophilized finished product is satisfactory.

18. **CONCLUSIONS/RECOMMENDATIONS:**
When acceptable EER is received, the application is approvable. An approval package will be prepared.

19. **REVIEWER:** Shing H. Liu, Ph.D.
**DATE COMPLETED/REVISED:** Completed 02/11/97

cc: ANDA 40-174
DUP JACKET
Division File
FIELD COPY

Endorsements:
HFD-625/SLiu/02/11/97
HFD-625/MSmela/02/12/97
x:\new\firmsam\gensia\40174CR3.APP
F/T by: gp/02/21/97

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 040174

## BIOEQUIVALENCE REVIEW(S)

ANDA 40-174

JUN 27 1996

Gensia Laboratories, Inc.
Attention: Donald J. Harrigan, R.Ph.
19 Hughes
Irvine, CA 92718-1902

Dear Mr. Harrigan:

This is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Leucovorin Calcium for Injection, 350 mg (base)/vial.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 20 1996

Leucovorin Calcium Injection
20 mg/mL Leucovorin Calcium
350 mg/Vial
ANDA #40-174
Reviewer: Moheb H. Makary
WP. 40174W.D95

Gensia Laboratories
Irvine, CA
Submission date
December 29, 1995

# Review a Request for Waiver

## I. Objective:

The firm requested waiver of bioequivalence study requirements for its product Leucovorin Calcium Injection, 20 mg/mL, 350 mg/vial. Innovator product is Leucovorin Calcium® for Injection (lyophilized) 350 mg/vial, manufactured by Immunex.

Leucovorin is one of several active, chemically reduced derivatives of folic acid. It is useful as an antidote to drugs which act as folic acid antagonists. Leucovorin Calcium for Injection is indicated for intravenous or intramuscular administration.

## II. Formulations:

The formulations of the proposed test product and reference product are shown below:

| | Reference Product Leucovorin Calcium for Injection 350 mg/Vial 20 mg/mL (Lyophilized) | Proposed Test Product Leucovorin Calcium Injection 350 mg/Vial 20 mg/mL (Lyophilized) |
|---|---|---|
| Contents per mL | | |
| Leucovorin (Leucovorin Calcium, USP) | 20 mg | 20 mg |
| Sodium Chloride | 8 mg | 8 mg |
| Sodium Hydroxide* | qs to pH adjust | qs to pH adjust |
| Hydrochloric Acid* | qs to pH adjust | qs to pH adjust |
| Water for Injection* | qs | qs |

* Used during formulation: Product is lyophilized.

## III. Comment:

As shown above, the proposed test product, Leucovorin Calcium Injection, 20 mg/mL, 350 mg/Vial contains the same active and inactive ingredients in the same quantities per mL as the reference product, Leucovorin Calcium® for Injection, 20 mg/mL,

350 mg/Vial. Waiver of in vivo bioequivalence study requirements may be granted based on 21 CFR 320.22 (b)(1).

IV. Recommendation:

The Division of Bioequivalence agrees that the information submitted by Gensia Laboratories, LTD, demonstrates that Leucovorin Calcium Injection 20 mg/mL, 350 mg/Vial, falls under Section 320.22 (b)(1) of Bioavailability/Bioequivalence Regulations. Waiver of in vivo bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation, Leucovorin Calcium Injection 20 mg/mL, 350 mg/Vial, manufactured by Gensia Laboratories, LTD, to be bioequivalent to Leucovorin Calcium® for Injection 350 mg/Vial manufactured by Immunex.

The firm should be informed of the above recommendation.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE /S/
FT INITIALLED RMHATRE Date: 6/18/96

/S/

Concur: Date: 6/20/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

MMakary/6-17-96 wp 40174W.D95
cc: ANDA #40-174, original, HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Makary), Drug File, Division File.

JUN 20 1996

Leucovorin Calcium Injection
20 mg/mL Leucovorin Calcium
350 mg/Vial
ANDA #40-174
Reviewer: Moheb H. Makary
WP. 40174W.D95

Gensia Laboratories
Irvine, CA
Submission date
December 29, 1995

## Review a Request for Waiver

I. Objective:

The firm requested waiver of bioequivalence study requirements for its product Leucovorin Calcium Injection, 20 mg/mL, 350 mg/vial. Innovator product is Leucovorin Calcium® for Injection (lyophilized) 350 mg/vial, manufactured by Immunex.

Leucovorin is one of several active, chemically reduced derivatives of folic acid. It is useful as an antidote to drugs which act as folic acid antagonists. Leucovorin Calcium for Injection is indicated for intravenous or intramuscular administration.

II. Formulations:

The formulations of the proposed test product and reference product are shown below:

| | Reference Product Leucovorin Calcium for Injection 350 mg/Vial 20 mg/mL (Lyophilized) | Proposed Test Product Leucovorin Calcium Injection 350 mg/Vial 20 mg/mL (Lyophilized) |
|---|---|---|
| Contents per mL | | |
| Leucovorin (Leucovorin Calcium, USP) | 20 mg | 20 mg |
| Sodium Chloride | 8 mg | 8 mg |
| Sodium Hydroxide* | qs to pH adjust | qs to pH adjust |
| Hydrochloric Acid* | qs to pH adjust | qs to pH adjust |
| Water for Injection* | qs | qs |

* Used during formulation: Product is lyophilized.

III. Comment:

As shown above, the proposed test product, Leucovorin Calcium Injection, 20 mg/mL, 350 mg/Vial contains the same active and inactive ingredients in the same quantities per mL as the reference product, Leucovorin Calcium® for Injection, 20 mg/mL,

350 mg/Vial. Waiver of in vivo bioequivalence study requirements may be granted based on 21 CFR 320.22 (b)(1).

IV. Recommendation:

The Division of Bioequivalence agrees that the information submitted by Gensia Laboratories, LTD, demonstrates that Leucovorin Calcium Injection 20 mg/mL, 350 mg/Vial, falls under Section 320.22 (b)(1) of Bioavailability/Bioequivalence Regulations. Waiver of in vivo bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation, Leucovorin Calcium Injection 20 mg/mL, 350 mg/Vial, manufactured by Gensia Laboratories, LTD, to be bioequivalent to Leucovorin Calcium® for Injection 350 mg/Vial manufactured by Immunex.

The firm should be informed of the above recommendation.

Moheb H. Makary

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE Ramaprasad M. Mhatre Date: 6/18/96

Concur: _____ Date: 6/20/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

MMakary/6-17-96 wp 40174W.D95
cc: ANDA #40-174, original, HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Makary), Drug File, Division File.